EXHIBIT B

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Tapas Mukhopadhyay, *et al.*

Serial No.: 10/043,877

Filed: January 9, 2002

For: ANTIHELMINTHIC DRUGS AS A TREATMENT FOR HYPERPROLIFERATIVE DISEASES

Group Art Unit: 1642

Examiner: B. J. Fetterolf

Atty. Dkt. No.: INRP:095US

CERTIFICATE OF MAILING
37 C.F.R. 1.8

I hereby certify that this correspondence is being deposited with the U.S. Postal Service with sufficient postage as First Class Mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date below:

October 28, 2004 — Date

Monica A. De La Paz

I. AMENDMENT; II. RESPONSE TO OFFICE ACTION DATED JUNE 28, 2004; AND III. PETITION FOR EXTENSION OF TIME

Mail Stop Amendment
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450 Commissioner:

This paper is submitted in response to the Office Action dated June 28, 2004 for which the three-month date for response was September 28, 2004.

A request for a one-month extension of time to respond is included herewith along with the required fee. This one-month extension will bring the due date to October 28, 2004, which is within the six-month statutory period. Should such request or fee be deficient or absent, consider this paragraph such a request and authorization to withdraw the appropriate fee under 37 C.F.R.

§§ 1.16 to 1.21 from Fulbright & Jaworski L.L.P. Account No.: 50-1212/INRP:095US. Please amend the application as follows.

Amendments to the claims begin on page 3 of this response.

Amendments to the Drawings begin on page 23 of this response and include both an attached replacement sheet and an annotated sheet showing changes.

Remarks start at page 24.

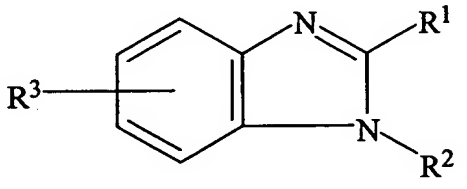
I. AMENDMENT

Listing of the Claims

The following listing of the claims replaces all previous listings or version of the claims:

1. (Original) A method for inducing apoptosis in a cell expressing a tumor suppressor gene comprising administering an effective amount of a benzimidazole to said cell, wherein the expression of the tumor suppressor gene by the cell and the benzimidazole results in the apoptosis of the cell.

2. (Original) The method of claim 1, wherein the benzimidazole is a derivative having the formula:



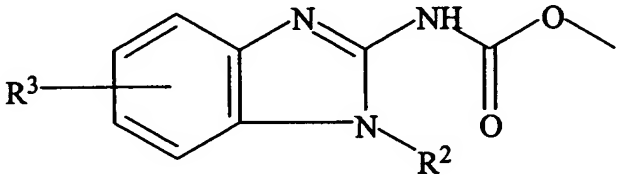
wherein R^3 is selected from the group consisting of H, carboxyl ($-CO_2H$), hydroxyl, amino, chloro, difluormethoxy, benzoyl, phenyl-thio, pyridinyl, propyl-thio, diphenyl, methoxy(methoxy-dimethyl,pyridinyl)methyl-(sulfonyl), fluorophenylmethyl-2-chloro, propenyl, chloroprophyl or esters ($-CO_2R^4$) wherein R^4 is selected from the group consisting of alkoxy, haloalkyl, alkenyl, and cycloalkyl, wherein the alkyl groups have from 1 – 8 carbons, or $CH_3CH_2(OCH_2CH_2)_n$–, or $CH_3CH_2CH_2(OCH_2CH_2CH_2)_n$—, or $(CH_3)_2CH(OCH(CH_3)CH_2)_n$—, wherein n is from 1 – 3, wherein R^1 is OH, Cl, SH, carbamate or piperidin-4-yl, and R^2 is hydrogen, α-methylvinyl, 3-chloropropyl or piperidin-4-yl, or the pharmaceutically effective organic or inorganic salts thereof, or mixtures thereof.

3. (Original) The method of claim 2, wherein the benzimidazole derivative is methyl 5-benzoylbenzimidazole-2-carbamate (mebendazole).

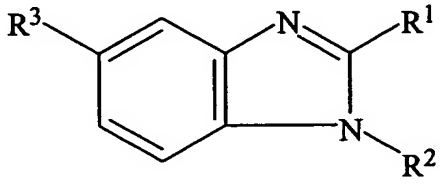
4. (Withdrawn) The method of claim 2, wherein the benzimidazole derivative is methyl 5-(phenylthio)- 2-benzimidazole carbamate (fenbendazole).

5. (Withdrawn) The method of claim 2, wherein the benzimidazole derivative is 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (omeprazole).

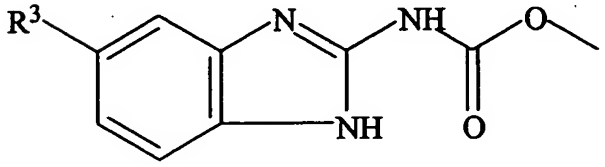
6. (Withdrawn) The method of claim 2, wherein the benzimidazole derivative is



7. (Withdrawn) The method of claim 2, wherein the benzimidazole derivative is



8. (Withdrawn) The method of claim 2, wherein the benzimidazole derivative is



9. (Original) The method of claim 1, wherein the dose of benzimidazole is at least 0.05 μg/ml.

10. (Original) The method of claim 1, wherein benzimidazole administration is repeated at least once.

11. (Withdrawn) The method of claim 1, wherein said method is used to treat rheumatoid arthritis, inflammatory bowel disease or restenosis.

12. (Original) The method of claim 1, wherein the cell is a tumor cell.

13. (Original) The method of claim 12, wherein the tumor cell is a multidrug resistant tumor cell.

14. (Original) The method of claim 13, wherein the multidrug resistant tumor cell is a lung tumor cell, a non-small cell lung carcinoma cell, a breast cancer cell, or a sarcoma cell.

15. (Original) The method of claim 12, wherein the tumor cell is a lung tumor cell.

16. (Original) The method of claim 15, wherein the lung tumor cell is a non-small cell lung carcinoma cell.

17. (Original) The method of claim 12, wherein the tumor cell is a breast cancer cell.

18. (Original) The method of claim 12, wherein the tumor cell is a sarcoma cell.

19. (Original) The method of claim 12, wherein the tumor suppressor gene is p53, p16, p21, Rb, p15, BRCA1, BRCA2, zac1, p73, ATM, HIC-1, DPC-4, FHIT, NF2, APC, DCC, PTEN, ING1, NOEY1, NOEY2, PML, OVCA1, MADR2, WT1, 53BP2, IRF-1, MDA-7 and C-CAM.

20. (Original) The method of claim 12, wherein the tumor suppressor gene is MDA-7.

21. (Original) The method of claim 12, wherein the tumor suppressor gene is p53.

22. (Currently Amended) The method of claim 12, further comprising the step of determining the tumor suppressor gene status of the tumor cell prior to the method of claim 1.

23. (Original) The method of claim 22, wherein determining comprises Southern blotting.

24. (Original) The method of claim 22, wherein determining comprises Northern blotting.

25. (Original) The method of claim 22, wherein determining comprises PCR.

26. (Original) The method of claim 22, wherein determining comprises ELISA.

27. (Original) The method of claim 22, wherein determining comprises Western blotting.

28. (Original) The method of claim 22, wherein determining comprises immunofluorescence.

29. (Original) The method of claim 12, wherein the tumor cell expresses a functional tumor suppressor gene.

30. (Withdrawn) The method of claim 12, further comprising tumor suppressor gene therapy.

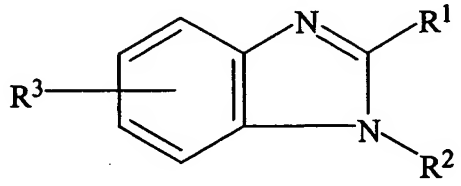
31. (Withdrawn) A method for inducing apoptosis in a cell comprising the steps of:

a) administering to the cell a vector comprising a polynucleotide sequence encoding a tumor suppressor gene operably linked to a transcription control region; and

b) administering to the cell an effective amount of a benzimidazole,

wherein the expression of the tumor suppressor gene by the cell and the administration of the benzimidazole results in the apoptosis of said cell.

32. (Withdrawn) The method of claim 31, wherein the benzimidazole is a derivative having the formula:



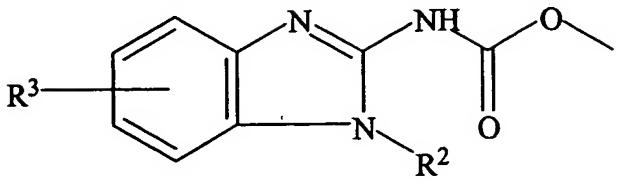
wherein R^3 is selected from the group consisting of H, carboxyl ($-CO_2H$), hydroxyl, amino, chloro, difluormethoxy, benzoyl, phenyl-thio, pyridinyl, propyl-thio, diphenyl, methoxy(methoxy-dimethyl,pyridinyl)methyl-(sulfonyl), fluorophenylmethyl-2-chloro, propenyl, chloroprophyl or esters ($-CO_2R^4$) wherein R^4 is selected from the group consisting of alkoxy, haloalkyl, alkenyl, and cycloalkyl, wherein the alkyl groups have from 1 – 8 carbons, or $CH_3CH_2(OCH_2CH_2)_n-$, or $CH_3CH_2CH_2(OCH_2CH_2CH_2)_n—$, or $(CH_3)_2CH(OCH(CH_3)CH_2)_n—$, wherein n is from 1 – 3, wherein R^1 is OH, Cl, SH, carbamate or piperidin-4-yl, and R^2 is hydrogen, α-methylvinyl, 3-chloropropyl or piperidin-4-yl, or the pharmaceutically effective organic or inorganic salts thereof, or mixtures thereof.

33. (Withdrawn) The method of claim 32, wherein the benzimidazole derivative is methyl 5-benzoylbenzimidazole-2-carbamate (mebendazole).

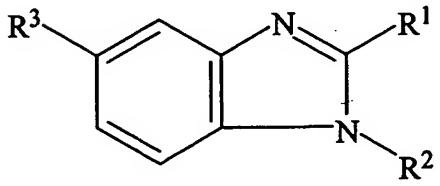
34. (Withdrawn) The method of claim 32, wherein the benzimidazole derivative is methyl 5-(phenylthio)-2-benzimidazole carbamate (fenbendazole).

35. (Withdrawn) The method of claim 32, wherein the benzimidazole derivative is 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (omeprazole)

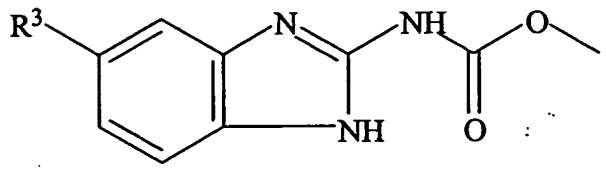
36. (Withdrawn) The method of claim 32, wherein the benzimidazole derivative is



37. (Withdrawn) The method of claim 32, wherein the benzimidazole derivative is



38. (Withdrawn) The method of claim 32, wherein the benzimidazole derivative is



39. (Withdrawn) The method of claim 31, wherein the tumor suppressor gene is p53, p16, p21, Rb, p15, BRCA1, BRCA2, zac1, p73, ATM, HIC-1, DPC-4, FHIT, NF2, APC, DCC, PTEN, ING1, NOEY1, NOEY2, PML, OVCA1, MADR2, WT1, 53BP2, IRF-1, MDA-7 and C-CAM.

40. (Withdrawn) The method of claim 31, wherein the tumor suppressor gene is MDA-7.

41. (Withdrawn) The method of claim 31, wherein the tumor suppressor gene is p53.

42. (Withdrawn) The method of claim 31, wherein said method is used to treat rheumatoid arthritis, inflammatory bowel disease or restenosis.

43. (Withdrawn) The method of claim 31, wherein the cell is a tumor cell.

44. (Withdrawn) The method of claim 43, wherein the tumor cell is a multidrug resistant tumor cell.

45. (Withdrawn) The method of claim 44, wherein the multidrug resistant tumor cell is a lung tumor cell, a non-small cell lung carcinoma cell, a breast cancer cell, or a sarcoma cell.

46. (Withdrawn) The method of claim 43, wherein the tumor cell is a lung tumor cell.

47. (Withdrawn) The method of claim 46, wherein the lung tumor cell is a non-small cell lung carcinoma cell.

48. (Withdrawn) The method of claim 43, wherein the tumor cell is a breast cancer cell.

49. (Withdrawn) The method of claim 43, wherein the tumor cell is a sarcoma cell.

50. (Withdrawn) The method of claim 31, wherein the vector is a virus.

51. (Withdrawn) The method of claim 50, wherein the virus is adenovirus, adeno-associated virus, herpesvirus, retrovirus, polyoma virus, vaccinia virus or lentivirus.

52. (Withdrawn) The method of claim 50, wherein the virus is an adenovirus.

53. (Withdrawn) The method of claim 52, wherein the adenovirus is replication defective.

54. (Withdrawn) The method of claim 52, wherein the adenovirus is lacking at least a portion of the E1B region.

55. (Withdrawn) The method of claim 31, wherein the tumor suppressor gene is under the control of a CMV IE promoter.

56. (Withdrawn) The method of claim 50, wherein the virus is an adeno-associated virus.

57. (Withdrawn) The method of claim 50, wherein the virus is a herpesvirus.

58. (Withdrawn) The method of claim 50, wherein the virus is a retrovirus.

59. (Withdrawn) The method of claim 50, wherein the virus is a polyoma virus.

60. (Withdrawn) The method of claim 50, wherein the virus is a vaccinia virus.

61. (Withdrawn) The method of claim 50, wherein the virus is a lentivirus.

62. (Withdrawn) The method of claim 31, wherein vector administration is repeated at least once.

63. (Withdrawn) The method of claim 31, wherein benzimidazole administration is repeated at least once.

64. (Withdrawn) The method of claim 31, wherein the dose of benzimidazole is at least 0.05 μg/ml.

65. (Withdrawn) The method of claim 43, further comprising the step of determining the tumor suppressor gene status of the tumor cell prior to method of claim 32.

66. (Withdrawn) The method of claim 65, wherein determining comprises Southern blotting.

67. (Withdrawn) The method of claim 65, wherein determining comprises Northern blotting.

68. (Withdrawn) The method of claim 65, wherein determining comprises PCR.

69. (Withdrawn) The method of claim 65, wherein determining comprises ELISA.

70. (Withdrawn) The method of claim 65, wherein determining comprises Western blotting.

71. (Withdrawn) The method of claim 65, wherein determining comprises immunofluorescence.

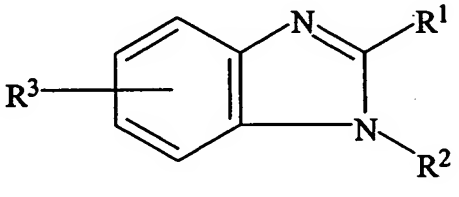
72. (Withdrawn) The method of claim 43, wherein the tumor cell expresses a functional endogenous tumor suppressor gene.

73. (Withdrawn) The method of claim 43, wherein the tumor cell expresses endogenous mutant tumor suppressor gene.

74. (Withdrawn) The method of claim 43, wherein the tumor cell expresses no endogenous tumor suppressor gene.

75. (Original) A method for treating a patient having cancer, wherein cancer cells express a tumor suppressor, comprising administering an effective amount of a benzimidazole to said patient, wherein the expression of the tumor suppressor gene by the cancer cell and the administration of the benzimidazole results in the inhibition of said cancer.

76. (Original) The method of claim 75, wherein the benzimidazole is a derivative having the formula:



wherein R^3 is selected from the group consisting of H, carboxyl ($-CO_2H$), hydroxyl, amino, chloro, difluormethoxy, benzoyl, phenyl-thio, pyridinyl, propyl-thio, diphenyl, methoxy(methoxy-dimethyl,pyridinyl)methyl-(sulfonyl), fluorophenylmethyl-2-chloro, propenyl, chloroprophyl or esters ($-CO_2R^4$) wherein R^4 is selected from the group consisting of alkoxy, haloalkyl, alkenyl, and cycloalkyl, wherein the alkyl groups have from 1 – 8 carbons, or $CH_3CH_2(OCH_2CH_2)_n-$, or

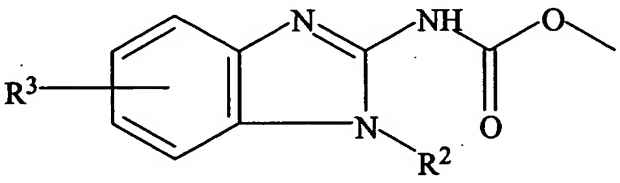
$CH_3CH_2CH_2(OCH_2CH_2CH_2)_n$—, or $(CH_3)_2CH(OCH(CH_3)CH_2)_n$—, wherein n is from 1 – 3, wherein R^1 is OH, Cl, SH, carbamate or piperidin-4-yl, and R^2 is hydrogen, α-methylvinyl, 3-chloropropyl or piperidin-4-yl, or the pharmaceutically effective organic or inorganic salts thereof, or mixtures thereof.

77. (Original) The method of claim 75, wherein the benzimidazole derivative is methyl 5-benzoylbenzimidazole-2-carbamate (mebendazole).

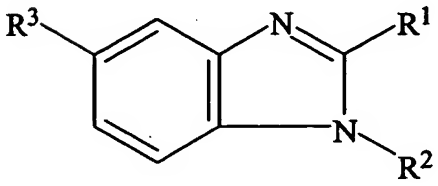
78. (Withdrawn) The method of claim 75, wherein the benzimidazole derivative is methyl 5-(phenylthio)-2-benzimidazole carbamate (fenbendazole).

79. (Withdrawn) The method of claim 75, wherein the benzimidazole derivative is 5 methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (omeprazole)

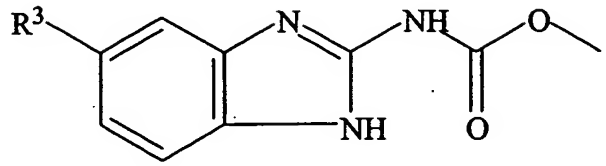
80. (Withdrawn) The method of claim 75, wherein the benzimidazole derivative is



81. (Withdrawn) The method of claim 75, wherein the benzimidazole derivative is



82. (Withdrawn) The method of claim 75, wherein the benzimidazole derivative is



83. (Original) The method of claim 75, wherein the tumor suppressor gene is p53, p16, p21, Rb, p15, BRCA1, BRCA2, zac1, p73, ATM, HIC-1, DPC-4, FHIT, NF2, APC, DCC, PTEN, ING1, NOEY1, NOEY2, PML, OVCA1, MADR2, WT1, 53BP2, IRF-1, MDA-7 and C-CAM.

84. (Original) The method of claim 75, wherein the tumor suppressor gene is MDA-7.

85. (Original) The method of claim 75, wherein the tumor suppressor gene is p53.

86. (Original) The method of claim 75, wherein the cancer cell is a multidrug resistant tumor cell.

87. (Original) The method of claim 86, wherein the multidrug resistant tumor cell is a lung tumor cell, a non-small cell lung carcinoma cell, a breast cancer cell, or a sarcoma cell.

88. (Original) The method of claim 75, wherein the cancer cell is a lung tumor cell.

89. (Original) The method of claim 88, wherein the lung tumor cell is a non-small cell lung carcinoma cell.

90. (Original) The method of claim 75, wherein the cancer cell is a breast cancer cell.

91. (Original) The method of claim 75, wherein the cancer cell is a sarcoma cell.

92. (Original) The method of claim 75, wherein benzimidazole administration comprises intratumoral administration.

93. (Original) The method of claim 75, wherein benzimidazole administration comprises systemic administration.

94. (Original) The method of claim 75, wherein benzimidazole administration comprises oral administration.

95. (Original) The method of claim 75, wherein benzimidazole administration comprises administration in the area local to a tumor in said patient.

96. (Original) The method of claim 75, wherein benzimidazole administration comprises administration in the area regional to a tumor in said patient.

97. (Original) The method of claim 75, wherein benzimidazole administration is repeated at least once.

98. (Original) The method of claim 75, wherein the dose of benzimidazole is about 0.1 mg per kg body weight.

99. (Original) The method of claim 75, wherein the dose of benzimidazole is about 1.0 mg per kg body weight.

100. (Currently Amended) The method of claim 83, further comprising the step of determining the tumor suppressor gene status of the cancer cell prior to the method of claim 75.

101. (Original) The method of claim 100, wherein determining comprises Southern blotting.

102. (Original) The method of claim 100, wherein determining comprises Northern blotting.

103. (Original) The method of claim 100, wherein determining comprises PCR.

104. (Original) The method of claim 100, wherein determining comprises ELISA.

105. (Original) The method of claim 100, wherein determining comprises Western blotting.

106. (Original) The method of claim 100, wherein determining comprises immunofluorescence.

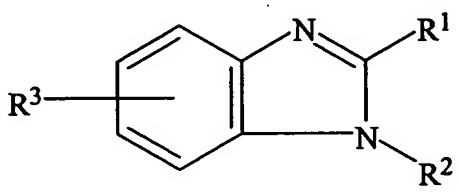
107. (Withdrawn) The method of claim 75, further comprising treating the patient with a second anti-cancer therapy selected from the group consisting of a chemotherapy, a radiotherapy, an immunotherapy, or a gene therapy.

108. (Withdrawn) A method of treating a patient having cancer comprising the steps of:

a) administering to said patient a vector comprising a polynucleotide sequence encoding a tumor suppressor gene operably linked to a transcription control region; and b) administering to said patient a therapeutically effective amount of benzimidazole,

wherein the expression of the tumor suppressor gene in a cancer cell and the administration of benzimidazole inhibits said cancer.

109. (Withdrawn) The method of claim 108, wherein the benzimidazole is a derivative having the formula:



wherein R^3 is selected from the group consisting of H, carboxyl (-CO_2H), hydroxyl, amino, chloro, difluormethoxy, benzoyl, phenyl-thio, pyridinyl, propyl-thio, diphenyl, methoxy(methoxy-dimethyl,pyridinyl)methyl-(sulfonyl), fluorophenylmethyl-2-chloro, propenyl,

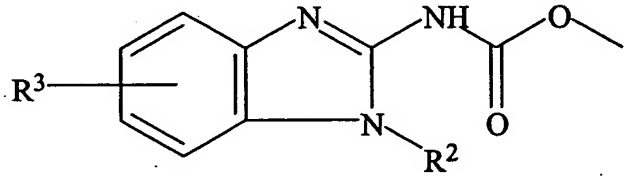
chloroprophyl or esters (-CO_2R^4) wherein R^4 is selected from the group consisting of alkoxy, haloalkyl, alkenyl, and cycloalkyl, wherein the alkyl groups have from 1 – 8 carbons, or $CH_3CH_2(OCH_2CH_2)_n$–, or $CH_3CH_2CH_2(OCH_2CH_2CH_2)_n$—, or $(CH_3)_2CH(OCH(CH_3)CH_2)_n$—, wherein n is from 1 – 3, wherein R^1 is OH, Cl, SH, carbamate or piperidin-4-yl, and R^2 is hydrogen, α-methylvinyl, 3-chloropropyl or piperidin-4-yl, or the pharmaceutically effective organic or inorganic salts thereof, or mixtures thereof.

110. (Withdrawn) The method of claim 109, wherein the benzimidazole derivative is methyl 5-benzoylbenzimidazole-2-carbamate (mebendazole).

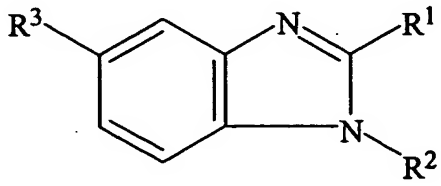
111. (Withdrawn) The method of claim 109, wherein the benzimidazole is methyl 5-(phenylthio)-2-benzimidazole carbamate (fenbendazole).

112. (Withdrawn) The method of claim 109, wherein the benzimidazole is 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (omeprazole)

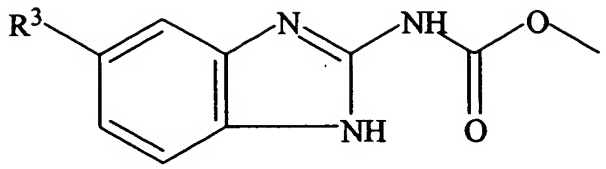
113. (Withdrawn) The method of claim 109, wherein the benzimidazole is



114. (Withdrawn) The method of claim 109, wherein the benzimidazole is



115. (Withdrawn) The method of claim 109, wherein the benzimidazole is



116. (Withdrawn) The method of claim 108, wherein the tumor suppressor gene is p53, p16, p21, Rb, p15, BRCA1, BRCA2, zac1, p73, ATM, HIC-1, DPC-4, FHIT, NF2, APC, DCC, PTEN, ING1, NOEY1, NOEY2, PML, OVCA1, MADR2, WT1, 53BP2, IRF-1, MDA-7 and C-CAM.

117. (Withdrawn) The method of claim 108, wherein the tumor suppressor gene is MDA-7.

118. (Withdrawn) The method of claim 108, wherein the tumor suppressor gene is p53.

119. (Withdrawn) The method of claim 108, wherein the cancer cell is a multidrug resistant tumor cell.

120. (Withdrawn) The method of claim 119, wherein the multidrug resistant tumor cell is a lung tumor cell, a non-small cell lung carcinoma cell, a breast cancer cell, or a sarcoma cell.

121. (Withdrawn) The method of claim 108, wherein the cancer cell is a lung tumor cell.

122. (Withdrawn) The method of claim 121, wherein the lung tumor cell is a non-small cell lung carcinoma cell.

123. (Withdrawn) The method of claim 108, wherein the cancer cell is a breast cancer cell.

124. (Withdrawn) The method of claim 108, wherein the cancer cell is a sarcoma cell.

125. (Withdrawn) The method of claim 108, wherein the vector is a virus.

126. (Withdrawn) The method of claim 125, wherein the virus is adenovirus, adeno-associated virus, herpesvirus, retrovirus, polyoma virus, or vaccinia virus.

127. (Withdrawn) The method of claim 125, wherein the vector is an adenovirus.

128. (Withdrawn) The method of claim 127, wherein the adenovirus lacks at least a portion of the E1B region.

129. (Withdrawn) The method of claim 127, wherein the adenovirus is replication defective.

130. (Withdrawn) The method of claim 108, wherein the polynucleotide sequence encoding the tumor suppressor gene is under the control of a CMV IE promoter.

131. (Withdrawn) The method of claim 125, wherein the virus is adeno-associated virus.

132. (Withdrawn) The method of claim 125, wherein the virus is a herpesvirus.

133. (Withdrawn) The method of claim 125, wherein the virus is a retrovirus.

134. (Withdrawn) The method of claim 125, wherein the virus is a polyoma virus.

135. (Withdrawn) The method of claim 125, wherein the virus is a vaccinia virus.

136. (Withdrawn) The method of claim 125, wherein the virus is a lentivirus.

137. (Withdrawn) The method of claim 108, wherein vector administration is repeated at least once.

138. (Withdrawn) The method of claim 108, wherein vector administration comprises intratumoral administration.

139. (Withdrawn) The method of claim 108, wherein vector administration comprises systemic administration.

140. (Withdrawn) The method of claim 108, wherein vector administration comprises administration in the area local to a tumor in said patient.

141. (Withdrawn) The method of claim 108, wherein vector administration comprises administration in the area regional to a tumor in said patient.

142. (Withdrawn) The method of claim 108, wherein benzimidazole administration comprises intratumoral administration.

143. (Withdrawn) The method of claim 108, wherein benzimidazole administration comprises systemic administration.

144. (Withdrawn) The method of claim 108, wherein benzimidazole administration comprises oral administration.

145. (Withdrawn) The method of claim 108, wherein benzimidazole administration comprises administration in the area local to a tumor in said patient.

146. (Withdrawn) The method of claim 108, wherein benzimidazole administration comprises administration in the area regional to a tumor in said patient.

147. (Withdrawn) The method of claim 108, wherein benzimidazole administration is repeated at least once.

148. (Withdrawn) The method of claim 108, wherein the dose of benzimidazole is about 0.1 mg per kg body weight.

149. (Withdrawn) The method of claim 108, wherein the dose of benzimidazole is about 1.0 mg per kg body weight.

150. (Withdrawn) The method of claim 108, further comprising the step of determining the tumor suppressor gene status of the cancer cell prior to method of claim 108.

151. (Withdrawn) The method of claim 150, wherein determining comprises Southern blotting.

152. (Withdrawn) The method of claim 150, wherein determining comprises Northern blotting.

153. (Withdrawn) The method of claim 150, wherein determining comprises PCR.

154. (Withdrawn) The method of claim 150, wherein determining comprises ELISA.

155. (Withdrawn) The method of claim 150, wherein determining comprises Western blotting.

156. (Withdrawn) The method of claim 150, wherein determining comprises immunofluorescence.

157. (Withdrawn) The method of claim 108, wherein the tumor cell expresses a functional endogenous tumor suppressor gene.

158. (Withdrawn) The method of claim 108, wherein the tumor cell expresses endogenous mutant tumor suppressor gene.

159. (Withdrawn) The method of claim 108, wherein the tumor cell expresses no endogenous tumor suppressor gene.

160. (Withdrawn) The method of claim 108, further comprising treating the patient with a second anti-cancer therapy selected from the group consisting of a chemotherapy, a radiotherapy, an immunotherapy, or a gene therapy distinct from the tumor suppressor provided.

161. (Currently Amended) A method for treating a patient with a hyperproliferative disorder comprising administering to said subject an amount of a benzimidazole ~~effect~~ effective to ~~kill or inhibit the growth of hyperproliferative cells within said~~ induce apoptosis of a cell in said patient.

162. (Currently Amended) The method of claim 161, wherein said ~~subject~~ patient suffers from cancer.

163. (Withdrawn) The method of claim 162, further comprising treating the patient with an anti-cancer therapy selected from the group consisting of a chemotherapy, a radiotherapy, an immunotherapy, or a gene therapy.

164. (Canceled)

165. (Canceled)

166. (Withdrawn) The method of claim 165, wherein said hyperproliferative disorder is rheumatoid arthritis, inflammatory bowel disease or restenosis.

167. (Canceled)

168. (Withdrawn) The method of claim 167, further comprising treating the patient with an anti-cancer therapy selected from the group consisting of a chemotherapy, a radiotherapy, an immunotherapy, or a gene therapy.

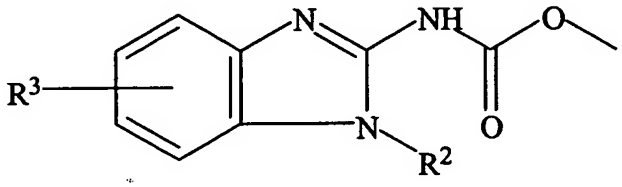
169. (Canceled)

170. (Canceled)

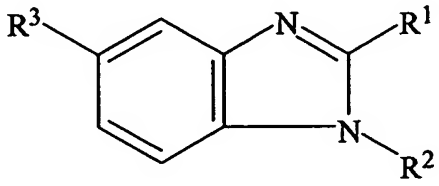
171. (Withdrawn) The method of claim 169, wherein the benzimidazole is methyl 5-(phenylthio)-2-benzimidazole carbamate (fenbendazole).

172. (Withdrawn) The method of claim 169, wherein the benzimidazole is 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (omeprazole)

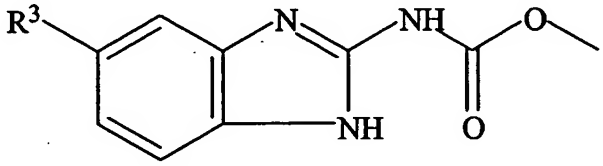
173. (Withdrawn) The method of claim 169, wherein the benzimidazole is



174. (Withdrawn) The method of claim 169, wherein the benzimidazole is



175. (Withdrawn) The method of claim 169, wherein the benzimidazole is



176-182. (Canceled)

Amendments to the Drawings:

The attached sheet of drawings includes changes to FIG. 1B. This sheet, which includes FIG. 1A-FIG. 1C, replaces the original sheet including FIG. 1A-FIG. 1C. In FIG. 1B, the labeling of fenbendazole and mebendazole was reversed, and this has now been corrected.

Attachment: Replacement Sheet
Annotated Sheet Showing Changes

II. RESPONSE TO OFFICE ACTION

A. Status of the Claims

The Action acknowledges Applicants' election, without traverse, of the Group I invention, drawn to methods of administering a benzimidazole to a cell, as exemplified by claims 1-29, 75-106, 161-162, 164-17, and 169-182. In this regard, the Action indicates that claims 1-3, 9-10, 12-29, 75-77, 83-106, 161-162, 164-165, 167, 169-170, and 176-182 are currently under consideration, and claims 4-8, 11-, 30-74, 78-82, 107-160, 163, 166, 168, and 171-175 are withdrawn from consideration as being drawn to a non-elected invention and/or species. Claims 22, 100, 161, and 162 have been amended in the amendment included with this response. Claims 164, 165, 167, 169-170, and 176-182 have been canceled without prejudice or disclaimer. No new claims have been added. The specification fully supports the claim amendments, which are discussed in detail below.

The Action notes that a provisional election of species is required under 35 U.S.C. §121, and indicates that Applicants' representative made a provisional election of species, without traverse, to prosecute the species of cancer as being the disease of interest and mebendazole as the benzimidazole derivate, with the following R group substitutions: R^3 – benzoyl, R^2 – H, and R^1 – carbamate, claims 3, 77, and 170. Applicants herein affirm this election of species.

B. The Claim Objection is Overcome

Claim 161 is objected to because the word "effect" does not appear to be used correctly. The claim has been amended to replace "effect" with "effective." As a result, claim 161 is now drawn to "[a] method for treating a patient with a hyperproliferative disorder comprising administering to said subject an amount of a benzimidazole ***effective*** to kill or inhibit the growth

of hyperproliferative cells within said patient." (emphasis added). Therefore, the objection to claim 161 has been overcome.

Applicants also note that claims 22 and 100 have been amended to correct omission of the word "the" from the claim language. Furthermore, claim 162 has been amended to recite "patient" instead of "subject," since this claim depends from a claim that recites "patient."

C. The Claim Rejections under 35 U.S.C. §112 are Overcome

Claims 22-29 and 100-106 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicants regard as the invention. In particular, the Action indicates that the term "status" as used in the claims is a "relative term" which renders the claim indefinite, since "status" could imply activity, class, type, progress, *etc.*, and as a result, one of ordinary skill would not be reasonably apprised of the scope of the invention. Office Action, page 3. Applicants respectfully traverse.

Claim 22 recites "the method of claim 12, further comprising the step of determining the tumor suppressor gene status of the tumor cell prior to the method of claim 1." Claims 23-28 are dependent claims of claim 22. Claim 100 recites "the method of claim 83, further comprising the step of determining the tumor suppressor gene status of the cancer cell prior to the method of claim 75." Claims 101-106 depend form claim 100.

The Action indicates that "[t]he term 'status' of the tumor suppressor gene in Claims 12 and 100 is a relative term, which renders the claim indefinite." Office Action, page 3. Since claim 12 does not recite "status," Applicants will assume that the reference to claim 12 was erroneous, and the Action meant to refer to claims 22 rather than claim 12. In addition, the

rejection is said to apply to claim 29. However, claim 29, which depends from claim 12, does not recite "status." Therefore, Applicants will assume that claim 29 was erroneously included in this rejection. If this is not the case, Applicants request clarification from the Examiner regarding the reason for rejection of claims 12 and 29.

"The essential inquiry pertaining to [the definiteness] requirement is whether the claims set out and circumscribe a particular subject matter with a reasonable degree of clarity and particularity." *Manual of Patent Examining Procedure (MPEP)*, §2173. In reviewing a claim for compliance with 35 U.S.C. §112, second paragraph, the Examiner must consider the claim as a whole to determine whether the claim apprises one of ordinary skill in the art of its scope and, therefore, serves the notice function required by 35 U.S.C. §112, second paragraph. See, *e.g.*, *Solomon v. Kimberly-Clark Corp.*, 216 F.3d 1372, 139, 55 USPQ2d 1279, 1283 (Fed. Cir. 2000).

The specification provides detail that is sufficient to apprise one of ordinary skill in the art of the scope of the claims as it pertains to "determining the tumor suppressor gene status." For example, page 4 line 28 through page 5, line 5 provides that:

> "In yet another embodiment, there is provided a method for treating a cancer in a patient comprising the steps of (a) determining the tumor suppressor gene status of a tumor cell in the patient; and (b) contacting the tumor cell with an amount of benzimidazole sufficient to induce apoptosis in the cell. Where the tumor suppressor gene status of the tumor cell is that it contains a functional tumor suppressor gene, further provision of tumor suppressor gene may be unnecessary. Where the tumor suppressor gene status of the tumor is that it lacks a functional tumor suppressor protein, the method further comprises the transfer of a wild-type tumor suppressor gene into the tumor cell." (emphasis added)

One of ordinary skill in the art would understand the above section of the specification to provide two examples of tumor suppressor gene status – a functional tumor suppressor gene and a gene that does not encode a functional tumor suppressor protein. Therefore, this section of the specification provides examples of what is meant by the "status" of a tumor suppressor.

Regarding methods of determination of tumor suppressor gene "status," page 14, lines 26-29 provide that "[t]he tumor suppressor status of the tumor cells can be determined using any conventional methods." Examples of such methods are described on page 15, line 20 through page 21, line 8, and include immunoassays, immunohistological assays, Southern and Northern blotting techniques, and techniques involving the polymerase chain reaction. Example 2, page page 59, line 14 through page 60, line 20 describes experimental studies using human cell lines derived from NSCLC origins "of differing p53 status" (page 60, lines 9-10) that were analyzed by a cell growth assay. It is noted that three cell lines were examined, one of which produced a mutant p53 protein (H322), a second which is a p53 gene deleted variant (H1299), and a third that carries wild-type p53 protein (H460). Therefore, one of ordinary skill in the art, from reading the above, would understand that "determining the status of a tumor suppressor gene" involves, for example, a determination of whether the tumor suppressor gene encodes any protein at all, and if such protein is encoded, whether it is a wild-type protein or an abnormal protein, such as a mutant protein. Therefore, in view of the detail provided in the specification, one of ordinary skill in the art, upon reading the claims at issue, would be apprised of the scope of the invention as it pertains to determining the status of a tumor suppressor gene.

The examiner makes the observation that "[t]he term 'status' could imply activity, class, type, progress, ect. [sic]." Office Action, page 4. By making such an observation, the Examiner seems to be indicating that alternative wording may be preferable. However, a fundamental principal contained in 35 U.S.C. §112, second paragraph, is that Applicants are their own lexicographers. *MPEP* §2173.01. Applicants may use functional language, alternative expressions, negative limitations, or any style of expression or format of claim which makes clear the boundaries of the subject matter for which protection is sought. *MPEP* §2173.01. It is

well-established that "[a] claim may not be rejected solely because of the type of language used to define the subject matter for which patent protection is sought." *In re Swinehart*, 439 F.2d 210, 160 USPQ 226 (CCPA 1971).

Because claims 22-29 and claims 100-106 clearly define the scope of the invention, the claims are in compliance with the requirement for definiteness of 35 U.S.C. §112, second paragraph. Therefore, Applicants respectfully request that the rejection of these claims under 35 U.S.C. §112, second paragraph, should be withdrawn.

D. The Rejections Under 35 U.S.C. §102(a) are Overcome

1. Nature of the Rejection

Claims 1-3, 9-10, 12-13, 19, 29, 75-77, 83-85, 92-99, 161-162, 164-165, 167, 169-170, and 176-182 are rejected under 35 U.S.C. §102(a) as being anticipated by Davis (WO 00/41669). Davis is said to teach a method for treating cancer and diseases associated with angiogenesis involving administration of 5(6)-substituted benzimidazole-2-carbamates, including mebendazole, to destroy newly formed vasculature. Davis is also said to teach that mebendazole reduces the tumor vasculature in tumor-bearing mice by 56%, and is also said to teach various routes of administration and a preferred daily dose range. The Action indicates that Davis does not specifically teach mebendazole inducing apoptosis in a cell expressing a tumor suppressor gene.

The Examiner also believes that there is anticipation because "inherently, the loss of blood supply to the surrounding cells including cells expressing a tumor suppressor gene would inherently lead to cellular death or apoptosis due to lack of nutrients and oxygen." Office Action, page 4. The Examiner further notes that "the claimed functional limitation of a tumor

cell expressing a tumor suppressor gene would be an inherent property of the tumor cell, as would be a tumor cell being multi-drug resistant." Office Action, page 5. Therefore, the Examiner, citing *Bristol-Myers Squibb Company v. Ben Venue*, 58 USPQ2d 1508 (CAFC 2001), asserts that there is inherent anticipation because "it does not appear that the claims language or limitations result in a manipulative difference in the methods steps when compared to the prior art." Office Action, page 5. Applicants respectfully traverse.

2. Davis Fails to Expressly or Inherently Describe Each Element of the Claimed Invention

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987). Inherent anticipation arises when "the prior art necessarily functions in accordance with, or includes, the claimed limitations." *Atlas Powder Co.*, 190 F.3d at 1347. (citing *In re King*, 801 F.2d 1324, 11326 (Fed. Cir., 1986); see also *Atlas Powder Co.*, 190 F.3d at 1347-48). Furthermore,

> "inherency ... may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.

Mehl/Biophile Int'l. Cor. V. Milgraum, 192 F.3d 1362, 1365 (Fed. Cir. 1999) (quoting *In re Oelrich*, 666 F.2d 578, 581 (CCPA 1981).

Davis discloses a particular group of 5(6)-substituted benzimidazole-2-carbamates that can be purportedly used for the treatment of neovascularization. The neovascularization

addressed in Davis is neovascularization due to various diseases, such as solid tumors, psoriasis, macular degeneration, and diabetic retinopathy. Davis, page 1, lines 7-16.

Claim 1 and dependent claims 2, 3, 9, 10, 12, 13, 19, and 29 include the limitation "administering an effective amount of a benzimidazole to said cell, wherein the expression of the tumor suppressor gene by the cell and the benzimidazole results in the apoptosis of the cell." Claims 75 and dependent claims 76, 77, 83-85, 92-99 include the limitation "administering an effective amount of a benzimidazole to said patient, wherein the expression of the tumor suppressor gene by the cancer cell and the administration of the benzimidazole results in the inhibition of said cancer." Amended claim 161 and dependent claims 162 include the limitation "administering to said subject an amount of a benzimidazole effective to induce apoptosis of a cell in said patient." Claims 164, 165, 167, 169, 170, and 176-182 have been canceled without prejudice or disclaimer. As discussed below, the claim limitations set forth in this paragraph are not expressly or inherently disclosed in Davis.

(1) Expression of a Tumor Suppressor Gene Not Disclosed in Davis

Davis fails to anticipate claims 1-3, 9-10, 12-13, 19, 29, 75-77, 83-85, 92-99 because it fails to disclose, either expressly or inherently, "administration of a benzimidazole, wherein expression of the tumor suppressor gene by the cell and the benzimidazole results in apoptosis of the cell" or "wherein the expression of the tumor suppressor gene by the cancer cell and the administration of the benzimidazole results in the inhibition of said cancer."

The Examiner admits that "the reference [Davis] does not specifically teach mebendazole inducing apoptosis in a cell expressing a tumor suppressor gene." Office Action, page 4, paragraph 4. The focus of Davis is on neovascularization, and there is no indication from Davis

or the Examiner that the neovascular tissue that is addressed in Davis expresses a tumor suppressor gene. As noted in Davis, there are many causes of neovascularization, such as tumors, psoriasis, rheumatoid arthritis, atherosclerosis, macular degeneration, diabetic retinopathy, etc. See Davis, page 30, lines 7-16. Thus, neovascularization can occur in the absence of a tumor. Davis provides no indication that expression of a tumor suppressor gene by neovascularization is inherent.

The Examiner's argument set forth in the Office Action appears to be based on the premise that in certain embodiments, the neovascularization addressed in Davis is neovascularization due to a solid tumor, and that expression of a tumor suppressor gene is an inherent feature of a solid tumor. As set forth above, to be an inherent feature, it must be the case that "the prior art necessarily functions in accordance with, or includes, the claimed limitations." *Atlas Powder Co.*, 190 F.3d at 1347. In short, the Examiner appears to be arguing that every tumor expresses a tumor suppressor gene. In support of this argument, the Examiner has cited no reference.

Applicants note that in accordance with 37 C.F.R. §1.104(c)(2), "[i]n rejecting claims for want of novelty or for obviousness, the examiner must cite the best references at his or her command." No such reference has been cited by the Examiner to support the allegation that all solid tumors that have neovascularization express a tumor suppressor gene. Therefore, the knowledge, if such knowledge is present, appears to be personal to the Examiner. 37 C.F.R. §1.104(C)(3), which provides that "[i]n rejecting claims the examiner . . . may rely upon facts within his or her knowledge." In accordance with 37 C.F.R. §1.104(d)(2), Applicants have the right to call for an affidavit by the Examiner setting forth the reasons for the rejection. Applicants now wish to assert their right to call for such an affidavit by the Examiner, setting

forth the basis for the Examiner's contention that the expression of tumor suppressor genes is an inherent feature of tumors. Further, the Examiner's affidavit "shall be subject to contradiction or explanation by the affidavits of the applicant." 37 C.F.R. §1.104(d)(2). Therefore, upon review of the Examiner's affidavit, Applicants may choose submit their own affidavits in response.

As set forth below, Applicants plan to submit a declaration of the present inventors under 37 C.F.R. §1.131 to show conception and reduction to practice of the claimed invention prior to January 14, 2000, the priority date of Davis. This declaration, which will be submitted shortly hereafter in a Supplemental Response to the Office Action, will include a statement from the present inventors that the expression of a tumor suppressor gene by a cell is not known to be a requirement for a cell to be a tumor cell because some tumor cells express a tumor suppressor gene, whereas others do not. The inventors will declare that some tumor cells express a mutant tumor suppressor gene. Therefore, expression of a tumor suppressor gene is ***not*** an inherent feature of a tumor cell.

In their declaration, the present inventors will set forth *in vitro* evidence demonstrating that tumor cell lines containing wild-type *p53* are highly sensitive to growth inhibition and apoptosis after benzimidazole administration. No such evidence of cytotoxicity of benzimidazoles on tumor cells has been demonstrated in Davis. At most, Davis shows growth inhibition of certain benzimidazole derivatives on cells that form neovascular membranes. These cells, which are not cancer cells, are separate and distinct from the cells that form the actual tumor. Specifically, the cells that form the tumor are cancer cells, whereas the cells that form the neovascular membrane that provides blood supply to the tumor are not cancer cells. Therefore, Davis fails to disclose, expressly or inherently, that tumor cells inherently express tumor suppressor genes. Furthermore, there is no disclosure in Davis pertaining to any of the tumor

suppressor genes mentioned in Applicants' claim 19. Therefore, Davis fails to anticipate claims 1-3, 9-10, 12-13, 19, 29, 75-77, 83-85, and 92-99.

(2) Apoptosis as a Result of Benzimidazole Administration Not Disclosed in Davis

Davis also fails to anticipate claims 1-3, 9-10, 12-13, 19, and 29, and 161-162 because it fails to expressly or inherently disclose administration of a benzimidazole resulting in apoptosis of a cell. As noted above, the Examiner alleges that "inherently, the loss of blood supply to the surrounding cells including cells expressing a tumor suppressor gene would inherently lead to cellular death or apoptosis due to lack of nutrients and oxygen." In essence the Examiner is claiming that closure or damage to a neovascular membrane that provides nutrients and oxygen to tumor cells inherently results in apoptosis of cells. In support of this contention, the Examiner cites no reference. Furthermore, there is no disclosure in Davis pertaining to apoptosis, nor any discussion of the mechanism of cell death in tumor cells (or any other cell type) as a result of benzimidazole administration. Therefore, as set forth above, Applicants herein assert their right under 37 C.F.R. §1.104(d)(2) to call for an affidavit by the Examiner setting forth the reasons for the rejection. As noted above, Applicants understand that they have the right under 37 C.F.R. §1.104(d)(2) to contradict the affidavit of the Examiner, and plan to assert that right pending review of the Examiner's affidavit.

Applicants herein note that apoptosis of tumor cells is not inherent following closure of or damage to neovascular membranes. As set forth above, Applicants will provide in a Supplemental Response to the Office Action a declaration of the inventors showing prior conception and reduction to practice of the claimed invention before the priority date of Davis. This declaration will include statements from the inventors to indicate that apoptosis is not an

inherent feature of cells following benzimidazole administration. The present inventors will include in their declaration a statement that there exists more than one mechanism of cell death, and these mechanisms include apoptosis, necrosis, and anoikis. The present inventors will declare that when a neovascular membrane associated with a tumor is damaged or occluded, it does not necessarily follow that tumor cell death due to apoptosis will result. For example, tumor cell death may be by necrosis. Indeed, as noted by the Examiner, "the prior art teaches (page 1) that for a 'solid tumour to grow it must develop its own blood supply upon which it depends critically from the provision of oxygen and nutrients; if this blood supply is mechanically shot off the tumour undergoes necrotic death." Office Action, pages 4-5. Thus, the Examiner acknowledges necrosis as a mechanism of tumor cell death following closure of or damage to neovascular membranes. Thus, apoptosis of tumor cells does not necessarily occur following damage to or closure of an associated neovascular membrane. Therefore, because Davis fails to expressly or inherently disclose apoptosis of a cell as a result of benzimidazole administration, claims 1-3, 9-10, 12-13, 19, and 29, and 161-162 are not anticipated.

Furthermore, Davis fails to teach the limitation of claim 10 and 181 of "wherein the benzimidazole administration is repeated at least once." Rather, Davis focuses on a single administration of the benzimidazole derivative. See Davis, page 13, line 1 through page 14, line 4.

(3) Multi-Drug Resistance Not Disclosed in Davis

Davis also fails to teach the limitation of claim 12, and dependent claims 13 and 29 that recites "wherein the tumor cell is a multidrug resistant tumor cell." According to the Examiner, a tumor cell being multi-drug resistant would be an inherent function of a tumor cell. Office Action, page 5. In support of this contention, the Examiner cites no reference. Furthermore,

there is no disclosure in Davis pertaining to multi-drug resistance. Therefore, as set forth above, Applicants herein assert their right under 37 C.F.R. §1.104(d)(2) to call for an affidavit by the Examiner setting forth the reasons for the rejection. As noted above, Applicants understand that they have the right under 37 C.F.R. §1.104(d)(2) to contradict the affidavit of the Examiner.

Applicants herein note that multi-drug resistance is not an inherent feature of tumor cells. In the above-referenced declaration to be submitted in a Supplemental Response to the Office Action, the present inventors will provide declaratory evidence that not all tumor cells are multi-drug resistant. In their declaration, the present inventors will declare that multi-drug resistance is an acquired trait and generally requires selection with cytotoxic drugs to render a tumor cell multi-drug resistant. Furthermore, the present inventors will cite literature which suggests that genetic polymorphism has an impact on drug resistance of tumor cells. Therefore, because not all tumor cells are necessarily multi-drug resistant, Davis fails to expressly or inherently anticipate claims 12, 13, 19, and 29.

(4) Davis Does Not Disclose Various Routes of Administration and Dosages

Davis proposes various routes of administration of its benzimidazole derivatives. See Davis, page 12, lines 4-15. However, it fails to include the limitation of "intratumor administration" (see Applicants' claim 92), administration in the area local to a tumor (see Applicants' claim 95) or in the area regional to a tumor (see Applicants' claim 96). Regarding dose of the benzimidazole, Davis fails to disclose a dose that is about 0.1 mg per kg body weight (see Applicants' claim 98) or a dose that is about 1.0 mg per kg body weight (see Applicants' claim 99). Rather, Davis teaches a vast range of possible doses, noted that "the precise dose will

be determined by the administering physician but in general daily dosages may be in the range of 0.001 to 100 mg/kg preferably 0.1 to 50 mg/kg." Davis, page 12, lines 20-22.

Therefore, in view of the arguments set forth above, Applicants have established that Davis fails to expressly or inherently describe claims 1-3, 9-10, 12-13, 19, 29, 75-77, 83-85, 92-99, and 161-162.

3. Applicants Have Demonstrated Reduction to Practice of the Claimed Invention Before Davis

Even if the Examiner alleges that Davis anticipates the claimed invention, such as allegation would be impermissible in view of the fact that the present inventors reduced to practice the claimed invention prior to January 14, 2000, the PCT filing date of Davis. Applicants are in the process of finalizing a declaration under 37 C.F.R. §1.131 to show reduction to practice of the claimed invention prior to January 14, 2000, the PCT filing date of Davis. Submission of this declaration with the present response to the Office Action is slightly delayed due to the fact that one of the inventors is presently residing in India. Applicants plan to file this declaration in a Supplemental Response to the Office Action as soon as this declaration has been executed.

In accordance with the requirement of 37 C.F.R. §1.131(b), Applicants will provide in their declaration a showing of facts of such character and weight as to establish reduction to practice prior to January 14, 2000. Reduction to practice will be shown by a description of experiments and results in a draft manuscript entitled "Antihelminthies Drugs are Potent Inducers of Apoptosis in Human Lung Cancer Cells: Involvement of Wild-Type p53 and p21 Kinase Inhibitor."

The draft manuscript, which was prepared prior to January 14, 2000, details studies conducted by the inventors pertaining to the effect of benzimidazoles, including fenbendazole and mebendazole, on the regulation of apoptosis in human lung cancer cells. The inventors studied the *in vitro* effect of fenbendazole and mebendazole on human lung cancer cells lines, and found that these drugs dramatically inhibited the growth of lung cancer cells in culture. Both fenbendazole and mebendazole showed an apoptotic effect on H460 cancer cells. Western blot analysis using specific antibodies against Bcl-2, Bcl-xl, BAX, RB, cdc2, Cdk2, Cyclin A, Cyclin D, and p53 demonstrated that benzimidazole treatment resulted in a dose and time dependent nuclear accumulation of wild-type p53, and no alteration in levels of any of the other proteins. Furthermore, the inventors studied the effect of benzimidazoles on a number of human cell lines, and found that only the cell lines containing the wild-type p53 were highly sensitive to growth inhibition and apoptosis after benzimidazole treatment. In contrast, cell lines carrying mutated p53 were quite resistant to the cytotoxic effect of the benzimidazoles. Restoration of wild-type p53 function made tumor cells more sensitive to benzimidazole-induced apoptosis. Therefore, these finding strongly suggest that a p53 dependent mechanism contributes to the cytotoxicity of benzimidazoles in human cancer cells. In view of this declaration, Davis will not be available as prior art either under 35 U.S.C. §102(a) or 35 U.S.C. §102(e).

In view of the comments set forth above, and further in view of this declaration, Applicants assert that the Examiner would have no basis for any allegation that Davis anticipates the claimed invention.

E. The Rejections Under 35 U.S.C. §103(a) are Overcome

Claims 1-3, 9-10, 12-29, 75-77, 83-106, 161-162, 164-165, 167, 169-170, and 176-182 are rejected under 35 U.S.C. §103(a) as being unpatentable over Davis in combination with Perdoma *et al.* (J. Cancer Res. Clin. Oncol. 124:10-18, 1998) and Camden (U.S. Patent 6,262,093). The teachings of Davis are discussed in the previous section. Perdoma is said to teach that determining the *p53* status could make it possible to predict the response to therapy in certain patients, and that the response to cisplatin *in vivo* of NSCLC tumor lines was dependent on p53 status. Camden is said to teach methods of treating cancer using various benzimidazole derivatives. Further, Camden is said to teach various types and examples of cancer. According to the Examiner, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to administer mebendazole to various tumor cells, and that it would have been *prima facie* obvious to determine the status of a tumor suppressor gene in a tumor cell prior to administering mebendazole, and that one of ordinary skill in the art would be motivated to do so with a reasonable expectation of success based on the teachings of these references. Applicants respectfully traverse.

In order to establish a *prima facie* case of obviousness, three basic criteria must be met: (1) the prior art reference (or references when combined) must teach or suggest all the claim limitations; (2) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (3) there must be a reasonable expectation of success. *Manual of Patent Examining Procedure* § 2142. See also *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q. 2d 1438 (Fed Cir. 1991) (emphasizing that the teaching or suggestion to make the claimed combination and the reasonable expectation of success must be both found in the prior

art, and not based on applicant's disclosure). It is important to note that all three elements must be shown to establish a *prima facie* case of obviousness. Thus, if one element is missing, a *prima facie* case of obviousness does not exist.

A *prima facie* case of obviousness has not been established by the Examiner because the prior art references cited by the Examiner do not teach or suggest all of the claim limitations. The arguments set forth above in response to the rejection of claims under 35 U.S.C. §102(a) are herein incorporated into this section. As set forth in the discussion pertaining to the rejections under 35 U.S.C. §102(a), Davis *et al.* fails to teach or suggest the limitation of administering an effective amount of a benzimidazole to a cell, such that expression of a tumor suppressor gene by the cell and the benzimidazole results in the apoptosis of the cell. Davis *et al.* also fails to teach or suggest the limitation of administering an effective amount of a benzimidazole to a cancer cell, such that expression of a tumor suppressor gene by the cancer cell and the administration of benzimidazole results in inhibition of the cancer. Davis also fails to teach or suggest administering to a subject with a hyperproliferative lesion an amount of a benzimidazole effective to induce apoptosis within a cell of the hyperproliferative lesion. Furthermore, as set forth above, Davis will not be available as prior art because Applicants will be submitted a declaration under 37 C.F.R.§1.131 executed by the present inventors demonstrating reduction to practice of their claimed invention prior to January 14, 2000, the priority date of Davis.

Furthermore, neither Camden nor Perdomo teach or suggest the missing limitations that are not disclosed in Davis. Camden pertains to methods of treating certain cancers through the administration of certain benzimidazole derivatives. There is no teaching in Camden or Perdomo pertaining to the benzimidazole derivatives of the claimed invention, including mebendazole. Furthermore, Camden does not pertain to methods for inducing apoptosis in cells, such as cells

expressing a tumor suppressor gene. Nor is there any indication in either of these references that administration of benzimidazole derivatives results in apoptosis of cells, such as cells expressing a tumor suppressor gene or cells of a hyperproliferative lesion.

Therefore, for the reasons set forth above, Applicants respectfully request that the rejection of all of the claims under 35 U.S.C. §103(a) should be withdrawn.

III. PETITION FOR EXTENSION OF TIME

Pursuant to 37 C.F.R. § 1.136(a), Applicants petition for an extension of time of one month to and including October 28, 2004, in which to respond to the Office Action dated June 28, 2004. Pursuant to 37 C.F.R. § 1.17, a check in the amount of $55.00 is enclosed, which is the process fee for a one-month extension of time. If the check is inadvertently omitted, or should any additional fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason relating to the enclosed materials, or should an overpayment be included herein, the Commissioner is authorized to deduct or credit said fees from or to Fulbright & Jaworski Deposit Account No. 50-1212/INRP:095US.

The Examiner is invited to contact the undersigned attorney at (512) 536-5639 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

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Date: October 28, 2004

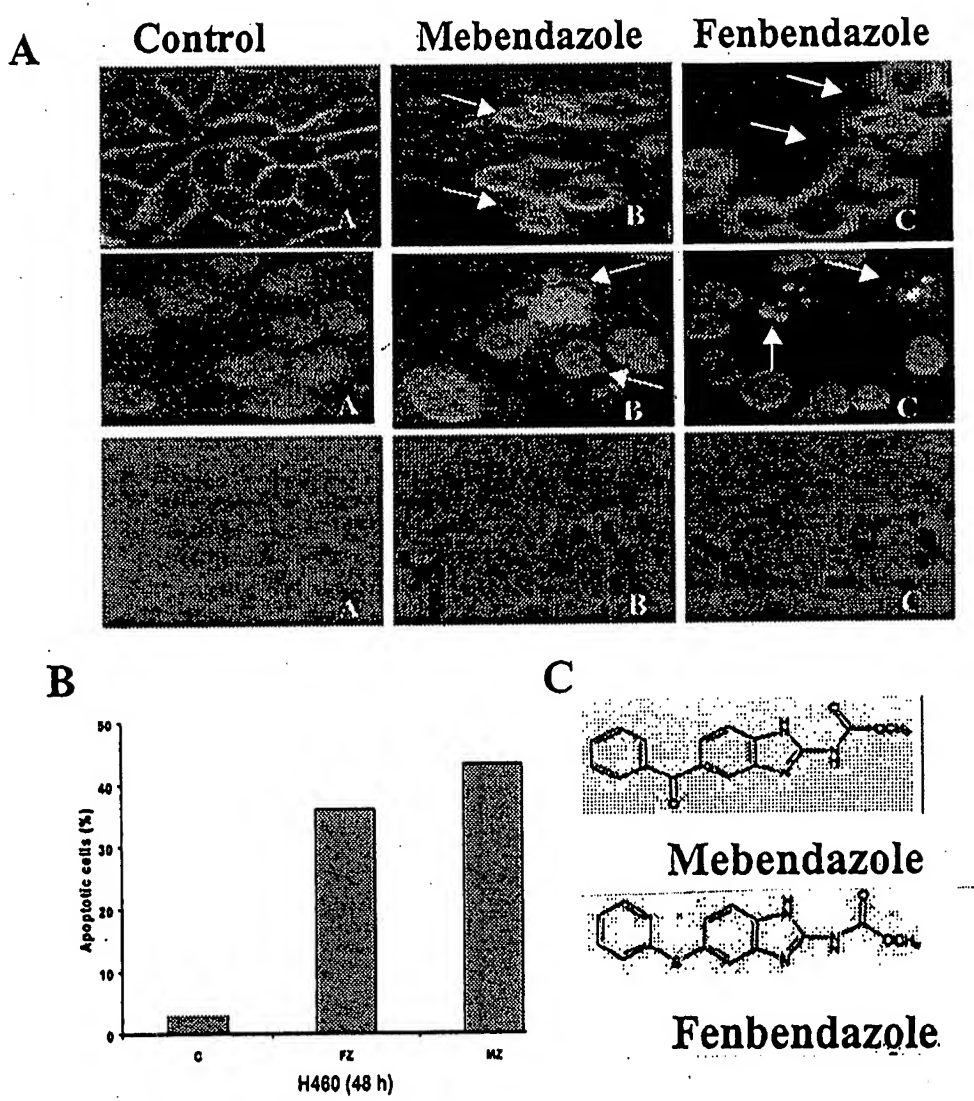

FIG. 1A - C

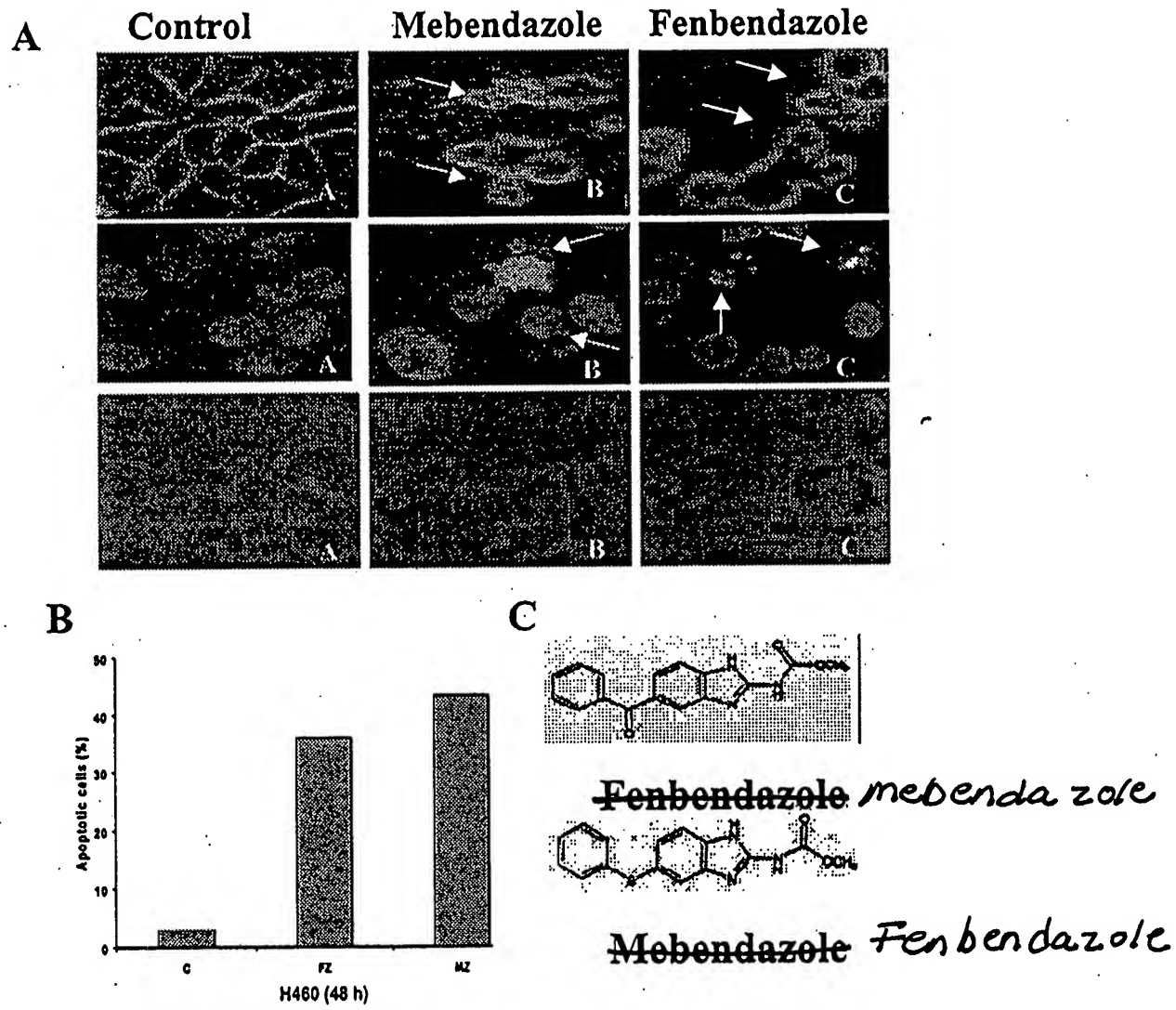

FIG. 1A - C